Statens legemiddelverk

FHI Folkehelseinstituttet

MedNytt Metodevarsling for helsetjenesten

Metodevarsel

1. Status og oppsummering

Autologous Ex-vivo Gene therapy for treatment of metachromatic leukodystrophy (MLD)

1.1 Oppsummering

Metoden omfatter et nytt virkestoff. Metoden har foreløpig ikke MT i Norge, EU eller i USA, men er under vurdering hos det Europeiske Legemiddelbyrået (EMA). Metoden er tilkjent orphan drug designation (legemiddel for en sjelden sykdom) (1).

1.2 Kort om metoden	1.3 Type metode	1.4 Finansieringsansvar	1.5 Fagfelt i MedNytt
ATC-kode: L Virkestoffnavn: *Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene.* Handelsnavn: Legemiddelform: *Autologous cells for infusion* MT-søker/innehaver: *Orchard Therapeutics*	☒ Legemiddel ☐ Diagnostikk ☐ Medisinsk utstyr ☒ Annet: Gene therapy	☒ Spesialisthelsetjenesten ☐ Folketrygd: blåresept ☐ Kommune ☐ Annet:	Neurology

1.6 Bestillingsanbefaling

Metodevurderinger

☐ Fullstendig metodevurdering
☒ Hurtig metodevurdering (CUA)
☐ Forenklet vurdering
☐ Avvente bestilling
☐ Ingen metodevurdering

Kommentar:

1.7 Relevante vurderingselementer for en metodevurdering

☒ Klinisk effekt relativ til komparator
☒ Sikkerhet relativ til komparator
☒ Kostnader / Ressursbruk
☒ Kostnadseffektivitet
☐ Juridiske konsekvenser
☐ Etiske vurderinger
☐ Organisatoriske konsekvenser
☐ Annet

Kommentar:

2. Beskrivelse av metoden

Sykdomsbeskrivelse og pasientgrunnlag

MLD is an ultra-rare and fatal inherited genetic disorder caused by mutations in the arylsulfatase A (*ARSA*) gene that result in deficiency of its corresponding enzyme. *ARSA* deficiency causes accumulation of sulfatides in the nervous system leading to microglial damage, progressive demyelination and neurodegeneration and subsequent loss of motor and cognitive functions and early death, especially in patients with early disease onset onset. [2,3,4]

Historically MLD has been classified into Late Infantile (LI) (40-60% of cases) [5], Juvenile (which is further sub-divided into Early Juvenile [EJ] and Late Juvenile [LJ]; 20-35% of cases) [5] and Adult variants (15-25% of cases) [5] based on the age of disease onset. [6,7] The underlying disease pathophysiology is common for all phenotypic forms of MLD, [8] and regardless of the clinical classification, the clinical course of the disease can be broadly divided into a pre-symptomatic stage with normal motor and cognitive development, followed by onset of first symptoms and a period of developmental plateau, which is short in early onset forms and longer and more variable in late onset forms. There is then a rapidly-progressing phase leading to a decerebrated state and eventually death for all phenotypic forms of the disease. [8,9,10]

Most patients with LI MLD die before the age of 5 (survival rate at 5 years from symptom onset is 25%, and survival rate at 10 years from symptom onset is zero).[11] For patients with Juvenile MLD (EJ and LJ) the survival rates at 5 and 10 years from symptom onset are 70% and 44%, respectively. [11]

For most patients with MLD, the approach is palliative in nature and involves physical therapy and anti-spasticity medications to maintain mobility and manage complications due to the bedridden status. The main focus of treatment, however, lies in the comprehensive care of patients, in the provision of aids and feeding tubes, in the prevention of pneumonia, pressure points, malnutrition, and medication for pain, spasticity, epilepsy, constipation, and restlessness play a role.[12] This palliative approach does not prevent the progressive deterioration of motor and cognitive outcomes in patients, nor the fatal outcomes of the disease. [13]

Allogeneic hematopoietic stem cell transplantation (alloHSCT) may be considered for a certain subset of patients, however the results are variable and evidence to date suggests that alloHSCT can neither effectively prevent the decline in motor and cognitive functions, nor change the fatal outcome of the disease.

The birth prevalence of MLD has been estimated at 1 per 100,000 births [3,14], which equates to approximately one new patient with MLD in Norway every 2 years (based on approximately 55,000 live births in Norway).

Libmeldy is an *ex-vivo* gene therapy aiming at correcting the genetic defect in MLD patients' own haematopoietic stem cells (HSCs). HSCs are taken from the patient, genetically modified outside of the body using a viral vector and then infused back into the patient where they engraft and deliver durable supraphysiological levels of the *ARSA* enzyme in the peripheral and central nervous system. The treatment pathway resembles that of haematopoietic stem cell transplantation (HSCT) and follows a similar process of bone marrow harvest, myeloablative conditioning and the administration of gene therapy.

Libmeldy is to be administered by a qualified and JACIE accredited specialist treatment centre with experience in delivering HSCT for neurometabolic patients,

Dagens behandling

Currently, there are no effective treatments for metachromatic leukodystrophy (MLD).
Drugs can be given to treat the symptoms as they occur, such as muscle spasms, infections, pain and seizures.

Virkningsmekanisme	Libmeldy (OTL-200) is an *ex-vivo* gene therapy aiming at correcting the genetic defect in MLD patients' own haematopoietic stem cells (HSCs). HSCs are taken from the patient, genetically modified outside of the body using a viral vector and then infused back into the patient where they engraft and deliver durable supraphysiological levels of the *ARSA* enzyme in the peripheral and central nervous system.
Tidligere godkjent indikasjon	None
Mulig indikasjon	Libmeldy is indicated for the treatment of metachromatic leukodystrophy (MLD): - in patients from birth to before 7 years of age, without clinical manifestations of the disease, with pathogenic biallelic mutations in the ARSA gene, - in patients with disease onset after 30 months and before 7 years of age, preserved cognitive and motor functions (IQ ≥ 85 and GMFC ≤ 1), with pathogenic biallelic mutations in the ARSA gene.
Kommentar fra FHI ved Companion Diagnostics [Dersom metoden dreier seg om companion diagnostics, skriver FHI om testen her]	☐ Metoden **vil medføre** bruk av ny diagnostisk metode (ny diagnostisk praksis) ☐ Metoden **vil ikke medføre** bruk av ny diagnostisk metode (allerede etablert diagnostisk praksis) Kommentar fra FHI:

3. Dokumentasjonsgrunnlag

3.1 Relevante og sentrale kliniske studier

Det foreligger klinisk dokumentasjon i form av minst en klinisk studie:

Populasjon (n=antall deltakere)	Intervensjon	Kontrollgruppe	Hovedutfallsmål	Studienummer, fase	Tidsperspektiv resultater
Male and female pediatric subjects with pre-symptomatic Early Onset MLD (Late Infantile (LI) to Early Juvenile (EJ) MLD) and early symptomatic EJ MLD. Total n=10. Age: up to 6 years	OTL-200 Single infusion Follow-up for 8 years	None	Open label, Non-randomised (single arm) This study will assess safety and efficacy of treatment using cryopreserved formulation of OTL-200 in pediatric subjects with pre-symptomatic Early Onset MLD (Late Infantile (LI) to Early Juvenile (EJ) MLD) and early symptomatic EJ MLD.	NCT03392987 205756 EudraCT: 2017-001730-26 Phase 2	Active; not recruiting
Male and female patients with Late Juvenile MLD Total n=6 Age: Child, Adult, Older Adult	OTL-200 Single infusion	None	Open label, single arm, non-randomised The aim of this clinical study is to assess the pharmacodynamic effect and long-term clinical efficacy and safety of OTL-200 in Late Juvenile MLD patients.	NCT04283227 OTL-200-07 EudraCT: 2019-002636-82 Phase 3	Recruiting
Male and females patients with early onset MLD aged up to 7 years (n=20)	OTL-200 Single infusion	None	Open label, single arm, non-randomised The aim of this study is to assess the safety and efficacy of OTL-200 in pediatric subjects with pre-symptomatic Early Onset MLD (Late Infantile (LI) to Early Juvenile (EJ) MLD) and early symptomatic EJ MLD.	NCT01560182 201222 EudraCT: 2009-017349-77 Phase 1 / 2	Active, not recruiting Ad hoc data published (15)

3.2 Metodevurderinger og –varsel

Metodevurdering ***- nasjonalt/lokalt -***	- Ingen relevante identifisert
Metodevurdering / systematiske oversikt ***- internasjonalt -***	- Det foreligger minst en relevant internasjonal metodevurdering eller systematisk oversikt (16,17).
Metodevarsel	- Det foreligger minst et relevant metodevarsel (18,19).

4. Referanser

1. Orphan designation for autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA for the treatment of metachromatic leukodystrophy (2007) https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307446
2. Bergner CG, van der Meer F, Winkler A, Wrzos C, Turkmen M, Valizada E, et al. Microglia damage precedes major myelin breakdown in X-linked adrenoleukodystrophy and metachromatic leukodystrophy. Glia 2019;67(6):1196-209.
3. Gieselmann V, Krageloh-Mann I. Metachromatic leukodystrophy--an update. Neuropediatrics 2010;41(1):1-6.
4. van Rappard DF, Boelens JJ, van Egmond ME, Kuball J, van Hasselt PM, Oostrom KJ, et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: the Dutch experience. Blood 2016;127(24):3098-101.
5. Wang RY, Bodamer OA, Watson MS, Wilcox WR. Lysosomal storage diseases: diagnostic confirmation and management of presymptomatic individuals. Genet Med 2011;13(5):457-84.
6. Kolodny E. Metachromatic leukodystrophy and multiple sulfatase deficiency: sulfatide lipidosis. In: CR S, AL B, WS S, D V, editors. The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York: McGraw-Hill; 1995. p. 2693-740.
7. von Figura K, Gieselmann V, Jaeken J. Metachromatic leukodystrophy. The metabolic & molecular bases of inherited disease. 2001.
8. Biffi A, Cesani M, Fumagalli F, Del Carro U, Baldoli C, Canale S, et al. Metachromatic leukodystrophy - mutation analysis provides further evidence of genotype-phenotype correlation. Clin Genet 2008;74(4):349-57.
9. Elgun S, Waibel J, Kehrer C, van Rappard D, Bohringer J, Beck-Wodl S, et al. Phenotypic variation between siblings with Metachromatic Leukodystrophy. Orphanet J Rare Dis 2019;14(1):136.
10. van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. Best Pract Res Clin Endocrinol Metab 2015;29(2):261-73.
11. Mahmood A, Berry J, Wenger DA, Escolar M, Sobeih M, Raymond G, et al. Metachromatic leukodystrophy: a case of triplets with the late infantile variant and a systematic review of the literature. J Child Neurol 2010;25(5):572-80.
12. Gomez-Ospina N. Arylsulfatase A Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; May 30, 2006.
13. Van Rappard DF, Boelens JJ, Wolf NI. Metachromatic leukodystrophy: Disease spectrum and approaches for treatment. Best Pract Res Clin Endocrinol Metab. 2015;29(2):261-273.
14. Krägeloh-Mann I, Groeschel S, Kehrer C, Opherk K, Nägele T, Handgretinger R, et al. Juvenile metachromatic leukodystrophy 10 years post transplant compared with a non-transplanted cohort. Bone Marrow Transplant 2013;48(3):369-75.
15. Sessa M, et al. Lentiviral haematopoietic stem-cell gene therapy in early onset metachromatic leukodystrophy: an ad-hoc analysis of a no-randomised, open label, phase 1 / 2 trial. Lancet 2016; 388:476-87.
16. Ashrafi MR, et al. An update on clinical, pathological, diagnostic, and therapeutic perspectives of childhood leukodystrophies. Expert Rev Neurother. 2020;20(1):65-84.
17. OTL-200 for treating metachromatic leukodystrophy (ID1666) [nettdokument]. London: National Institute for Health and Care Excellence. Proposed (GID-HST10028). [oppdatert 6. april 2020; lest 23. april 2020]. Tilgjengelig fra: https://www.nice.org.uk/guidance/proposed/gid-hst10028/documents
18. Autologous lentiviral ARSA gene therapy [nettdokument]. Specialist Pharmacy Service, NHS. [oppdatert 7. januar 2020; lest 15. april 2020]. Tilgjengelig fra: https://www.sps.nhs.uk/medicines/arsa-gene-therapy/
19. OTL-200 for Metachromatic Leukodystrophy. Newcastle upon Tyne, UK: NIHR Innovation Observatory; 2019. Health Technology Briefing NIHRIO ID 23997.

5. Versjonslogg

5.1 Dato	5.2 Endringer gjort i dokument
22.05.2020	Laget metodevarsel
DD.MM.ÅÅÅÅ	Endret dokumentasjonsgrunnlag basert på nytt søk av DD.MM.ÅÅÅÅ
DD.MM.ÅÅÅÅ	Endret status for metoden